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Targeting the Molecular Defect in *BRCA*-Deficient Tumors for Cancer Therapy

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Targeted therapies exploiting specific molecular defects in cancer cells promise to overcome roadblocks in the development of effective anticancer drugs. A recent report in the *New England Journal of Medicine* on the early clinical evaluation of Olaparib in cancers lacking the *BRCA1* or *BRCA2* genes exemplifies this promising new trend.

Developing drugs that are clinically effective against cancer remains almost as risky, protracted, and expensive today as it was a decade ago, defying earlier optimism that rapid advances in our understanding of cancer biology might dramatically alter this trend. One major barrier has been the difficulty in defining the clinical settings in which new agents will be effective. This has led to high rates of attrition when drug candidates that successfully pass Phase I trials (assessing safety and tolerability) are progressed through later-phase trials that test their clinical efficacy. Approaches targeting molecular defects that drive specific forms of cancer offer an exciting springboard to jump the "efficacy barrier." New drugs that inhibit oncogenic pathways essential for tumor outgrowth can achieve dramatic therapeutic outcomes (e.g., Demetri et al., 2002; Slamon et al., 2001), and careful matching of existing therapies to the genetic make-up of a tumor can considerably improve efficacy (e.g., Hegi et al., 2005). Fong and colleagues now further exemplify this exciting trend through the results of a Phase I clinical trial testing Olaparib, a potent inhibitor of the DNA repair enzyme poly-ADP ribose polymerase 1 (PARP1), in cancers lacking the *BRCA1* or *BRCA2* genes (Fong et al., 2009).

Genetic analyses of families exhibiting a high incidence of breast and ovarian cancer led to the identification of *BRCA1* and *BRCA2* in 1994 and 1995 (reviewed in Szabo and King, 1995). These studies found that the inheritance of heterozygous germline mutations in either one of these genes predispose carriers to cancer with a risk approaching 50%–70% by the age of ~60 years. The second allele is consistently lost in the cancers arising in these individuals; however, other tissues remain heterozygous for the inherited mutations.

Over a decade's studies from many laboratories have illuminated the biological function of the *BRCA* gene products and their role in cancer predisposition (reviewed in Venkitaraman, 2009), thus blazing the trail for clinical exploitation. BRCA proteins bind and colocalize with the eukaryal recombination enzyme RAD51, regulating its cellular localization and activity—a first clue to their indispensable function in homologous DNA recombination. This pathway normally works to restart DNA replication forks stalled at template lesions; therefore, its inactivation in BRCA-deficient cells leads to the collapse of stalled forks (e.g., Lomonosov et al., 2003), triggering DNA breakage and cell death when exposed to replication-blocking or DNA cross-linking agents. PARP1 inhibitors spectacularly exploit this defect unveiled by BRCA inactivation (Bryant et al., 2005; Farmer et al., 2005); in this setting, it is proposed they create single-strand DNA gaps at the sites of base lesions, stalling replication forks and leading to cytotoxic double-stranded DNA breaks. In vitro, these compounds are 2 to 3 orders of magnitude more lethal for homozygously BRCA-deficient cells than their wild-type or heterozygous counterparts.

Fong and colleagues have now undertaken a Phase I trial of Olaparib. In addition to assessing the drug's safety, tolerability, and pharmacology, they used a design that helped to give early indications of its efficacy. Thus, after the traditional dose-escalation stage to establish the maximum tolerated dose, Fong et al. expanded their trial to enrich for patients who carried germline mutations in *BRCA1* or *BRCA2* to test the hypothesis that the drug would elicit an antitumor response in this cohort. All of the 60 participants had received previous treatments; about half had tumors associated with cancer predisposition in *BRCA* mutation carriers. Sixteen of the 21 ovarian cancer patients, 3 of the 9 breast cancer patients, and 1 of the 3 prostate cancer patients carried *BRCA* mutations. Three additional patients either had a family history strongly indicative of *BRCA*-mutation-carrier status or were known mutation carriers who had cancers at atypical sites. Thus, overall, the trial compared 23 patients with *BRCA* mutations, suffering predominantly from cancers of the ovary, breast, or prostate, with 37 noncarrier patients whose malignancies largely originated in other tissues (e.g., colorectal cancer and melanoma).

Olaparib was well tolerated when administered as a single agent, compared to conventional chemotherapeutic regimes. Safety considerations, as well as pharmacokinetic and pharmacodynamic evaluation, led to the continuous administration of 200 mg, twice daily, being adopted for the majority of patients in the expansion stage of the trial, when the clinical efficacy of Olaparib was assessed.

The preliminary evaluation of antitumor responses achieved using Olaparib showed very encouraging results. Of the 23 *BRCA* mutation carriers, 2 could not be evaluated for clinical reasons and 2 who had tumors not typically associated with BRCA-deficiency progressed despite receiving Olaparib. Ten of the 19 remaining patients (53%) showed an objective antitumor response according to RECIST

criteria and/or >50% reduction in the serum markers CA-125 or PSA in patients with ovarian or prostate cancer, respectively, sustained for >4 weeks. Two further mutation carriers had evidence of stable disease. In contrast, no objective responses were observed in patients who were noncarriers of *BRCA* mutations.

These preliminary results strongly suggest that PARP1 inhibitors, even used as single agents, will be clinically effective in treating breast, ovarian or prostate carcinoma associated with germline *BRCA* mutations. Further clinical investigation will be needed to confirm this and to optimize dosing for particular clinical indications. It is encouraging in this latter context that *BRCA* mutation carriers exhibited no higher frequency or severity of adverse events than noncarriers, suggesting that Olaparib selectively affects cells that have lost both *BRCA* alleles, over heterozygously mutant but otherwise normal cells. Also, there appears to be a generous window between the minimum dose required to demonstrate a sustained pharmacodynamic effect (at doses >60 mg twice daily, there was sustained inhibition of PARP1 activity in peripheral blood mononuclear cells by ~90%) and the maximum tolerated dose (~400 mg twice daily), leaving headroom for further optimization.

Nonetheless, why were >35% of tumors in *BRCA* mutation carriers unresponsive to Olaparib? Several explanations are notionally possible. In vitro evidence suggests that the degree of sensitivity to PARP inhibition may depend on the degree to which homologous DNA recombination is compromised in *BRCA* mutant cells; this may vary according to not only the specific *BRCA* gene mutation and residual function, but also other genetic alterations in the cancer cells. Reversion of *BRCA* gene functions associated with the emergence of resistance to therapy has been observed in experimental systems; since all of the patients in this trial had received prior treatments, presumably including replication-blocking or DNA cross-linking agents, it is possible that reversion had been selected out in some cases. Last but not least, tumor exposure to Olaparib could conceivably differ between different cases due to patient or cancer characteristics.

The absence of serious adverse events is very promising. One caveat, however, is that this trial has so far assessed relatively short exposures to Olaparib in the majority of patients. Whether longer-term or chronic toxicities will emerge due to the systemic suppression of PARP1-dependent DNA repair, which acts to resolve lesions generated endogenously in many normal cells, needs to be assessed. One result concerning pharmacodynamics in the report is salient in this regard. The investigators examined cells in hair follicles plucked from the eyebrow of patients exposed to Olaparib for the presence of nuclear γH2AX foci, a reliable marker of double-stranded DNA breaks. These cells in *BRCA*-mutation carriers are expected to be heterozygous for the mutation, whereas in noncarriers, they have wild-type *BRCA* genes. However, Olaparib exposure rapidly induced DNA breakage in these cells, with the kinetics and magnitude of this response paralleling the pharmacokinetics of the drug. This suggests that PARP1 inhibition causes genotoxic lesions in normal as well as *BRCA*-deficient cancer cells but triggers cell death only in the latter, perhaps due to their failure to repair the lesions.

This intriguing result raises questions requiring further consideration. First, will the therapeutic window for Olaparib be as favorable with chronic as opposed to short-term treatment, or with increased drug exposure? This question comes from the possibility that there may be a low but significant frequency of misrepair, or even lack of repair, of Olaparib-induced lesions in nontumor cells. Second, will the selectivity of Olaparib be compromised if it were to be combined with other DNA-damaging or DNA-repair-inhibiting drugs? Such combinations could conceivably potentiate Olaparib-induced DNA breaks or modify their repair.

An interesting possibility discussed by Fong et al. is that Olaparib might prove to be useful in the treatment of cancers that occur in individuals without germline *BRCA* mutations but exhibit defects in homologous recombination. This is of potential importance because *BRCA* mutations are found in only a small minority of breast and ovarian cancers. This clinical trial provides no evidence so far to support this notion. Despite the caveat that the trial involved only a small number of patients, the results suggest defective homologous DNA recombination may be uncommon in ovarian and other tumors in nonmutation carriers used as controls.

Like all good studies, the work of Fong et al. raises as many questions as it answers. Nonetheless, it represents an important step in the evolution of rationale-driven, targeted cancer therapies from the laboratory to the clinic.

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